HFD-613/OGD

NDA 50-467/S-063
NDA 50-629/S-007

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, Michigan 4900 1

MAR 4 1999

Attention: Kathy A. Steindler
Regulatory Manager

Dear Ms. Steindler:

Please refer to your supplemental new drug applications dated January 21, 1998, received February 6, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Adriamycin RDF (doxorubicin hydrochloride for injection, USP), lyophilized powder and Adriamycin PFS (doxorubicin hydrochloride for injection, USP), preservative free solution.

We acknowledge receipt of your submissions dated January 2 1, 1998. These supplemental new drug applications provide for the following:

1. A Pediatric Use Supplement was submitted for NDA 50-467, Adriamycin RDF (doxorubicin hydrochloride for Injection, USP) and NDA 50-629, Adriamycin PFS (doxorubicin hydrochloride, USP), in consideration of the labeling requirements as stated in 21 CFR 201.57(f)(9). The revised package insert incorporated the following changes:

   a. Change the word "children" to "pediatric patients" in the WARNINGS and ADVERSE REACTIONS sections of the insert.

   b. In the WARNINGS section, Paragraph 1, Line 2, delete "and potentially" and replace with "or" to provide a stronger warning. Fatal congestive heart failure in pediatric patients months to years after doxorubicin therapy have been identified (References 1-7).

   c. In the WARNINGS sections, Paragraph 2, Line 2, insert ",exposure at an early age," after "cyclophosphamide therapy". Several publications indicate that exposure to doxorubicin at an early age increases the risk of eventually developing cardiotoxicity (References 8- 13).

   d. Add a Pediatric Use subsection to the PRECAUTIONS section that states the following: "Pediatric patients are at increased risk for developing delayed

cardiotoxicity. Follow-up cardiac evaluations are recommended periodically to monitor for this delayed cardiotoxicity (see WARNINGS)." Five publications support the recommendation for periodic monitoring (References 14- 18).

2. Additional editorial changes.

We also acknowledge receipt of your submissions dated July 27, 1998. These amendments provide for the following revisions to the original supplements in response to our June 4, 1998 facsimile transmission:

1. The trade dress was modified so that the established name is directly below the trade name as we recommended.

2. In the Warning Box, at the end of the 2nd Warning as a sentence, "Pediatric patients are at increased risk for developing delayed cardiotoxicity.", was added.

3. In the Clinical Pharmacology section, end of 1st paragraph as a new sentence, "Cells treated with doxorubicin have been shown to manifest the characteristic morphologic changes associated with apoptosis or programmed cell death. Doxorubicin-induced apoptosis may be an integral component of the cellular mechanism of action relating to therapeutic effects, toxicities, or both.", was added.

4. In the Clinical Pharmacology section, after paragraph 4 as a new paragraph, " Following administration of 10 to 75-mg/m^2 doses of doxorubicin to 60 children and adolescents ranging from 2 months to 20 years of age, doxorubicin clearance averaged 1443 +/- 114 mL/min/m^2. Further analysis demonstrated that clearance in 52 children greater than 2 years of age (1540 mL/min/m^2) was increased compared with adults. However, clearance in infants younger than 2 years of age (813 mL/min/m^2) was decreased compared with older children and approached the range of clearance values determined in adults.", was added.

5. In the Warnings section, Monitoring Cardiac Function subsection, end of 5th paragraph as a new sentence, "Pediatric patients receiving concomitant doxorubicin and actinomycin-D have manifested acute 'recall' pneumonitis at variable times after local radiation therapy.", was added.

6. In the Precautions section, Carcinogenesis, Mutagenesis, Impairment of Fertility subsection, end of 3rd paragraph as a new sentence, "Pediatric patients treated with doxorubicin or other topoisomerase II inhibitors are at a risk for developing acute myelogenous leukemia and other neoplasms. The extent of increased risk associated with doxorubicin has not been precisely quantified.", was added.

7. In the Precautions section, Pediatric Use subsection, after paragraph 1 as a new paragraph, "Doxorubicin, as a component of intensive chemotherapy regimens administered to pediatric patients, may contribute to prepubertal growth failure and gonadal impairment which is usually temporary.", was added. However, the new paragraph should be stated as "Doxorubicin, as a component of intensive chemotherapy regimens administered to pediatric patients, may contribute to prepubertal growth failure. It may also contribute to gonadal impairment, which is usually temporary."

8. In the Adverse Reactions section, Hematologic subsection, as the last sentence, "Pediatric patients are also at risk of developing secondary acute myeloid leukemia.", was added.

9. In the Handling and Disposal section, after the 2nd paragraph as a new paragraph, "Caregivers of pediatric patients receiving doxorubicin should be counseled to take precautions (such as wearing latex gloves) to prevent contact with the patient's urine and other body fluids for at least 5 days after each treatment.", was added.

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the above referenced labeling text with the revision noted in number 7. Accordingly, these supplemental applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted July 27, 1998) with the revision noted in number 7. In addition, references 1 through 8 in the References section should be deleted and replaced accordingly with the updated list of references which pertain to the handling of antineoplastic agents. The superscripts should also be revised to reflect these changes. Marketing the products with FPL that is not identical to the approved labeling text may render the products misbranded and unapproved new drugs.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed to each application. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplement NDA 50-467/S-063, 50-629/S-007." Approval of these submissions by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Patrick Guinn, Project Manager, at (301) 594-5767.

Sincerely,

Julie Beitzel for Robert Justice MD
3/4/99

Robert L. Justice
Acting Director
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research